ORIGINAL ARTICLE

Tumour, Node and Metastasis Stage, Tumour Grade, Lymph Node Ratio, Surgical Margin, and Oestrogen Receptor Status are Significant Predictors of Breast Cancer Recurrence

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ABSTRACT

Introduction: Prognostic factors play a crucial role in shaping treatment decisions as outlined in breast cancer clinical guidelines. Despite extensive large-scale cohort studies on the risks of prognostic factors for breast cancer recurrence, local research on this subject has been comparatively limited. This study aimed to identify the risk of prognostic factors associated with breast cancer recurrence. **Materials and methods:** This retrospective study examined prognostic factors, including age at diagnosis, tumour stage and grade, lymph node ratio (LNR), surgical margin status, lymphovascular invasion (LVI), hormone receptor status, and treatment received in 184 breast cancer patients. Recurrence-free survival (RFS) was evaluated using Kaplan-Meier analysis, and multivariate Cox regression analysis was applied to assess the risk of breast cancer recurrence. **Results:** Sixty patients (32.6%) experienced breast cancer recurrence, with a median recurrence time of 18 months. Kaplan-Meier analysis demonstrated that TNM stage III, pT3 stage, grade 3, high LNR (>0.65), positive surgical margin, presence of LVI, negative ER and PR status, and surgery alone without any adjuvant treatment were all associated with significantly worse RFS ($p < 0.05$). Multivariate Cox regression analysis revealed that TNM stage II and grade 3 tumour, high LNR, positive surgical margin, and negative ER status were independent prognostic factors for breast cancer recurrence. **Conclusion:** Higher TNM stage, higher tumour grade, high LNR, positive surgical margin, and negative ER status are significant predictors of breast cancer recurrence. Recognising these prognostic factors provides valuable insights for shaping future treatment approaches.
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INTRODUCTION

In 2021, the World Health Organisation (WHO) reported that breast cancer is the most commonly diagnosed cancer and the fifth most common cause of cancer-related deaths among women globally. This highlights the significance of breast cancer as a global health issue. The disease significantly affects individuals and healthcare systems, underscoring the urgent need for comprehensive prevention, early detection, and treatment approaches. In Malaysia, the Malaysia National Cancer Registry reported a worsening trend in newly diagnosed breast cancer cases, increasing from 17.7% during the period from 2012 to 2016 compared to 19.0% in the earlier period from 2007 to 2011(1). Despite this, the disease-free survival of breast cancer patients has increased tremendously over the last few decades, particularly when diagnosed at an early stage due to advances in the management. However, breast cancer recurrence remains the principal cause of breast cancer-related death. Recurrence can occur locally (in the breast and chest wall), regionally (axillary, supraclavicular, or infraclavicular lymph nodes) or distantly (bone, liver, lung, brain, or other lymph nodes). Local studies in Malaysia reported a wide range of recurrence rates, from 10 to 41.9% (2, 3), and suggested that nearly 50% of patients experience recurrence within 25 months (3).

Several studies have examined prognostic factors associated with breast cancer recurrence, including age at diagnosis, tumour size, grade and stage, lymph node involvement, lymphovascular invasion (LVI) and hormonal receptors, such as oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor 2 (HER2). The French E3N cohort (Etude Epidйmiologique auprиs de femmes de la Mutuelle

Générale de l'Education Nationale) study revealed that cases with high-grade tumours, larger tumour size, axillary nodal involvement, and negative ER and PR status exhibited a higher risk of recurrence or death (4). The findings were supported by another study by Yazdani A. et al. (5) and by a meta-analysis by Harahap WA et al. (6)

In the North Borneo experience, Raynee K. et al. (7) found that lymph node involvement and a higher lymph node ratio (LNR) were significant predictors of recurrence, while tumour stage, grade, size, and type were highly significant predictors of survival rates following surgical treatment. Additionally, Sae R.C. et al. (8) identified LVI, negative PR status, and positive CK5/6 expression as independent variables predictive of worse disease-free survival. In contrast, Mahno et al. (3) emphasised the independent association of tumour size, lymph node positivity, and LVI with breast cancer recurrence.

A meta-analysis study in 2017 reported that even after five years of adjuvant endocrine therapy, women with ER-positive, early-stage breast cancer still faced a persistent risk of recurrence and death from breast cancer for at least 20 years after diagnosis. Long-term follow-up strategies and the extension of endocrine therapy were suggested. (9) Another study in 2015 revealed that neoadjuvant chemotherapy and adjuvant hormone therapy were associated with improved recurrence-free survival. (10)

Understanding these associations is crucial for developing accurate predictive models to help clinicians predict disease recurrence and implement personalised treatment strategies. This research aims to contribute valuable insights into the factors influencing breast carcinoma recurrence and to guide the management of this prevalent cancer, ultimately improving patient outcomes.

MATERIALS AND METHODS

Sample

This retrospective cohort study reviewed clinicopathological data from breast cancer patients diagnosed at Hospital Kuala Lumpur between January 2019 and December 2020. Of the 560 patients diagnosed during this period, 184 met the study's inclusion criteria, which included stage I, II, or III invasive breast cancer patients who underwent mastectomy or breast-conserving surgery with axillary clearance. Additionally, the patients needed to adhere to the treatments and have at least two years of follow-up post-surgery. Patients with concurrent primary cancer, metastatic disease at diagnosis, those who had received neoadjuvant chemotherapy, or had incomplete clinical data were excluded.

Clinicopathological data, including prognostic factors of breast cancer such as age at diagnosis, tumour stage and grade, LNR (the ratio of the number of positive lymph nodes to the total excised axillary lymph nodes), surgical margin, LVI, hormonal receptor status (ER, PR and HER2) and treatments received were collected. The study aimed to determine recurrence-free survival (RFS) (the time from surgery to the first recurrence or last date follow-up) for these prognostic factors and assess their risk of breast cancer recurrence. Breast cancer recurrence was classified as early (≤24 months) or late (>24 months). Patients without signs of recurrence during the last clinic follow-up were considered as censored observations.

Statistical analysis

The collected data were analysed using SPSS software version 29. The frequency of total and recurrent cases for the prognostic factor variables was determined.

The study used Kaplan-Meier analysis to assess RFS and a log-rank test to determine the significant differences between the prognostic factor variables. A p-value < 0.05 was regarded as statistically significant.

The survival analysis using multivariate Cox regression analysis was conducted to examine the effect of multiple prognostic variables, allowing for the simultaneous assessment of several covariates on the hazard or risk of breast cancer recurrence. The adjusted hazard (AHR) ratio and 95% confidence interval (CI) were calculated for each variable. An adjusted hazard ratio above or below 1.00 suggests a high or low risk of recurrence, respectively. A p-value of less than 0.05 was considered statistically significant.

Ethical approval

The study was approved by the Medical Research Ethics Committee Malaysia (NMRR ID-23-00694-6SF).

RESULTS

A total of 560 Malaysian female patients diagnosed with breast cancer between 2019 and 2020 were identified at Hospital Kuala Lumpur. However, only 184 patients who met the criteria were enrolled in this research. The mean age was 54.84 years (SD 11.272, 95% CI). The majority of the patients were Malay (61.4%), followed by Indian (21.2%) and Chinese (17.4%). Most patients were in stage II (51.1%) disease (Table I).

Table I: The frequency of total and recurrence of prognostic factors in breast cancer.

Characteristic	Total (N=184)	Recurrent (n=60)	No recurrent (n=124)
Age (years)			
≤ 50	56 (30.4)	22 (36.7)	34 (27.4)
>50	128 (69.6)	38 (63.3)	90 (72.6)
Ethnicity			
Malay	113 (61.4)	43 (71.7)	70 (56.5)
Chinese	32 (17.4)	9 (15.0)	23 (18.5)
Indian	39 (21.2)	8 (13.3)	31 (25.0)
TNM stage			
Stage I	39 (21.2)	3 (5.0)	36 (29%)
Stage II	93 (50.5)	27 (45.0)	66 (53.2)
Stage III	52 (28.3)	30 (50.0)	22 (17.7)
pT stage			
pT1	56 (30.4)	9 (15.0)	47 (37.9)
pT2	94 (51.1)	33 (55.0)	61 (49.2)
pT3	25 (13.6)	13 (21.7)	12 (9.7)
pT4	9 (4.9)	5 (8.3)	4 (3.2)
Tumour grade			
Grade 1	38 (20.7)	3 (5.0)	35 (28.2)
Grade 2	70 (38.0)	17 (28.3)	53 (42.7)
Grade 3	76 (41.3)	40 (66.7)	36 (29.0)
Lymph node ratio			
Low (≤0.20)	136	31 (51.7)	105 (84.7)
Intermediate (0.21 – 0.65)	33	18 (30.0)	15 (12.1)
High (>0.65)	15	11 (18.3)	4 (3.2)
Margin involvement			
Yes	10 (5.4)	8 (13.3)	2 (1.6)
No	174 (94.6)	52 (86.7)	122 (98.4)
Lymphovascular invasion (LVI)			
Present	53 (28.8)	27 (45.0)	26 (21.0)
Absent	131 (71.2)	33 (55.0)	98 (79.0)
Oestrogen receptor (ER)			
Positive	115 (62.5)	22 (36.7)	93 (75.0)
Negative	69 (37.5)	38 (63.3)	31 (25.0)
Progesterone receptor (PR)			
Positive	78 (42.2)	17 (28.3)	61 (49.2)
Negative	106 (57.6)	43 (71.7)	63 (50.8)
HER2 expression			
Positive	39 (21.2)	16 (26.7)	23 (18.5)
Negative	145 (78.8)	44 (73.3)	101 (81.5)
Type of surgery			
MAC	124 (67.4)	42 (70.0)	82 (66.1)
BCS	60 (32.6)	18 (30.0)	42 (33.9)
Treatment modalities			
Surgery only	16 (8.7)	13 (21.7)	3 (2.4)
Surgery + chemotherapy ± radiotherapy ± hormone ± targeted therapy	117 (63.6)	42 (70.0)	75 (60.5)
Surgery + radiotherapy ± hormone ± targeted therapy	24 (13.0)	1 (1.7)	23 (18.5)
Surgery + hormone therapy	27 (14.7)	4 (6.7)	23 (18.5)

HER2 = Human epidermal growth factor receptor 2, MAC = mastectomy , BCS = breast conserving surgery

The minimum duration of follow-up was 24 months, with a median of 37 months (IQR=10, 95% CI). During the follow-up, 60 patients (32.6%) developed recurrence, with a median time to recurrence of 18 months (IQR: 18, CI: 95%). Within the recurrence group, 70% of the cases occurred within 24 months after surgery. Local recurrence comprised the majority of the first site of recurrence (53.4%). In contrast, regional and distant recurrences occurred in 33.3% and 13.3% of cases, respectively (Table II).

Table II: Distribution of time and sites of breast cancer recurrence

Time of recurrence	n (%) N=60
Early (≤24 months)	42 (70.0)
Late (>24 months)	18 (30.0)
Sites of recurrence	
Local	32 (53.4)
- Ipsilateral chest wall	26 (43.3)
- Breast	6 (10.0)
Regional	20 (33.3)
- Axillary tail	1 (1.7)
- Axillary lymph node	10 (16.7)
-Supraclavicular lymph node	7 (11.7)
- Infraclavicular lymph node	2 (3.3)
Distance	8 (13.3)
- Brain	4 (6.7)
- Lung	1 (1.7)
- Liver	1 (1.7)
- Bone (Femur)	1 (1.7)
- Gluteus	1 (1.7)

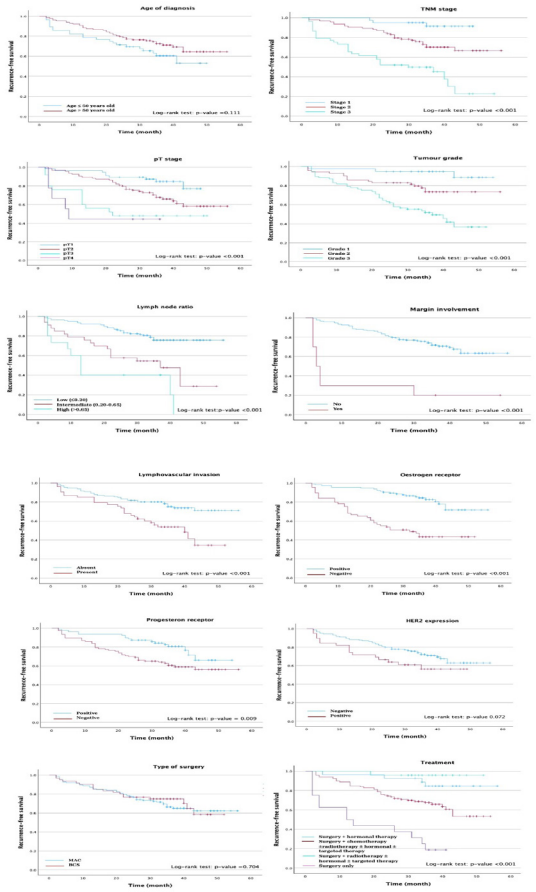

Figure 1: Kaplan Meier curves show the recurrence-free survival of the prognostic factors in breast cancer.

The Kaplan Meier analysis (Figure 1) revealed that TNM stage III, pT3 stage, grade 3, high lymph node ratio (>0.65), positive surgical margin, presence of LVI, negative ER and PR status, and surgery alone without any adjuvant treatment were all associated with significantly worse RFS, as evidenced by significant log-rank test results ($p<0.05$). HER2-positive cases and younger age group (≤50 years old) also showed the worst RFS; however, no significant differences were observed within these groups. The type of surgery also showed no significant difference in RFS.

In the multivariable Cox regression analysis (Table III), the hazard ratio showed statistically significant differences for stage II, grade 3, high lymph node ratio, positive surgical margin, and negative ER tumours. All types of treatment showed no significant difference. In this analysis, patients with stage II and III disease have a significantly higher risk of recurrence than those with stage I, with hazard ratios of 4.16 and 3.78, respectively. This suggests that individuals with stage II and III tumours are over four and three times more likely to experience recurrence. Even though stage III disease

showed an increased recurrence risk compared to stage I, the association was not statistically significant (HR: 3.78, 95% CI: 0.89 - 16.05, p = 0.071). However, this may still warrant clinical attention due to the substantial hazard ratio.

Table III: Multivariable Cox regression analysis on the risk of breast cancer recurrence

Characteristics	Adjusted Hazard Ratio (AHR)	95% Confidence interval	P value
TNM stage			
Stage I	Reference		
Stage II	4.16	1.24- 13.98	**0.021**
Stage III	3.78	0.89 – 16.05	0.071
Tumour grade			
Grade 1	Reference		
Grade 2	2.38	0.64 – 8.89	0.196
Grade 3	5.30	1.55 – 18.07	**0.008**
Lymph node ratio			
Low (≤0.20)	Reference		
Intermediate (0.20 – 0.65)	2.38	0.64 – 8.88	0.092
High (>0.65)	5.69	1.96 – 16.50	**0.001**
Positive surgical margin	12.20	4.58 – 32.42	**< 0.001**
Negative oestrogen receptor (ER)	4.07	2.13 – 7.77	**<0.001**
Treatment			
Surgery + hormone therapy	Reference		
Surgery + chemo-therapy ± radiother-apy ± hormone ± targeted therapy	0.56	0.56 – 0.16	0.352
Surgery + radiother-apy ± hormone ± targeted therapy	0.23	0.02 – 2.09	0.189
Surgery only	2.93	0.89 – 16.05	0.099

Backward stepwise Cox Regression Analysis model applied.
AHR: >1.00= high risk, and <1.00= low risk of recurrence

Grade 3 tumours have a significantly higher risk of recurrence than Grade 1, with a hazard ratio of 5.30 (95% CI: 1.55 - 18.07, p = 0.008). Grade 2 tumours also have an increased hazard ratio compared to Grade 1, but the association is not statistically significant (HR: 2.38, 95% CI: 0.64 - 8.89, p = 0.196). However, there is still a notable trend toward increased recurrence risk.

A high LNR is associated with a higher risk of recurrence than a low LNR, with a hazard ratio of 5.69 (95% CI: 1.96 - 16.50, p = 0.001). Patients with an intermediate LNR also show an increased hazard ratio compared to those with a low ratio, but it is not statistically significant (HR: 2.38, 95% CI: 0.64 - 8.88, p = 0.092). Nonetheless, there is a notable trend indicating a higher recurrence risk.

Patients with a positive surgical margin have a significantly higher risk of recurrence, with a strikingly high hazard ratio of 12.20 (95% CI: 4.58 - 32.42, p < 0.001). This suggests that individuals with positive surgical margins are over twelve times more likely to experience recurrence.

Additionally, negative-ER tumours show a significantly higher recurrence hazard than positive-ER tumours, with a hazard ratio of 4.07 (95% CI: 2.13 - 7.77, p < 0.001). This indicates that individuals with negative ER tumours are over four times more likely to experience recurrence.

Surgery combined with multiple therapies shows a lower risk of recurrence compared to surgery alone, which presents nearly three times the risk. However, this difference is not statistically significant when compared to other treatment groups.

DISCUSSION

The study focused on assessing the risk of breast cancer recurrence and the significance of prognostic factors as predictors of recurrence. Among the 184 patients analysed, 32.6% experienced a recurrence, with a median time of 18 months. Comparatively, three local studies reported recurrence rates between 10% and 41.9% (2, 3, 7). The variation in recurrence rates can be attributed to factors such as differences in patient demographics, comorbidities, cancer stage at diagnosis, treatment modalities and compliance, healthcare quality, follow-up duration, study design, and tumour biology.

The study also found that 53.3% of recurrent cases were localised, with 70% occurring within 24 months after surgery. These findings were consistent with the study by Marco et al. (2015), which reported the highest annual hazard of recurrence during the first five years, peaking between the first and second years at 15.2% (11). These results underscore the importance of vigilant monitoring and proactive management of recurrence risk, particularly in the early post-treatment phase for breast cancer patients.

The multivariate analysis identified high tumour stage, high tumour grade, high lymph node ratio, positive surgical margins, and negative ER status as independent predictors of increased recurrence risk. These findings highlight the importance of predicting recurrent events in breast cancer patients and emphasise the critical role of these factors in risk assessment and management. They also underscore the need for optimal management and close monitoring of high-risk patients, such as those with lymph node metastasis, larger tumour size, high-grade tumour, positive or close tumour margins, triple-negative breast cancer, and those who have received incomplete or suboptimal treatment.

High tumour stage

The TNM staging system, endorsed by the American

Joint Committee on Cancer (AJCC), is widely recognised as the most clinically useful system for staging cancers. A study by Orucevic et al.(2015) asserted that traditional TNM staging remains a relevant and predictive tool for breast cancer outcomes, even with the emerging prognostic influence of tumour biomarkers such as ER/PR/HER2 (12). In this study, stage II and III breast cancer were associated with a higher recurrence risk compared to the reference group (stage I), which aligns with previously mentioned studies. This underscores the continued relevance and prognostic value of the AJCC TNM staging system in predicting outcomes for breast cancer patients.

High tumour grade

Grade 3 tumours demonstrated a significantly higher risk compared to grade 1 ($p = 0.023$). This finding aligns with the study by Rothschild et al., where grade 3 tumours were significantly associated with early recurrence ($p < 0.0001$) (13). These results underscore the importance of considering tumour grade when assessing prognosis and treatment options. Higher-grade tumours are more aggressive due to rapid tumour cell proliferation, often leading to a poorer prognosis.

Lymph node involvement and high lymph node ratio

Lymph node status is widely regarded as a key prognostic factor in breast cancer and is commonly used to guide adjuvant, local, or systemic treatment decisions. Lymph node metastasis indicates a more aggressive tumour with greater invasive potential, and it is associated with an increased risk of both local and distant recurrence, leading to a poorer prognosis. However, the LNR offers a more nuanced and accurate prediction of breast cancer recurrence and prognosis than the traditional nodal staging by accounting for variability in lymph node sampling. This provides better risk stratification and reflects the tumour's biological behaviour more effectively.

Gorobets et al. concluded that classifying by the number of positive nodes did not adequately distinguish prognostic groups, whereas using the LNR provided a clear separation. A high LNR was associated with a higher risk of poor outcomes, while a low LNR correlated with risk and survival comparable to node-negative cases (14). The LNR proved to be a stronger predictor of recurrence and survival than nodal staging in stage II–III breast cancer patients. Notably, the risk of recurrence increased nearly 30-fold in patients with an LNR greater than 0.65 (15).

Positive surgical margin

In our study, a positive surgical margin was identified as a significant predictor of breast cancer recurrence. (AHR: 12.20, 95% CI: 4.58-32.42, $p < 0.001$). This finding aligns with the study by James R.B et al. (2022), which reported that positive or close margins were associated with higher risks of distant recurrence, local recurrence, and lower overall survival compared to negative or wide margins. (16) The consistency between these studies emphasises the critical importance of margin status in determining the likelihood of recurrence in breast cancer patients. A positive margin indicates the presence of residual malignant cells, thereby increasing the risk of local recurrence due to incomplete tumour removal,

Oestrogen receptor status

Consistent results from multiple studies underscore the prognostic significance of hormone receptor status. A positive hormonal receptor status is associated with a more favourable prognosis, while a negative ER status correlates with shorter survival and a higher hazard ratio compared to a positive ER status, demonstrating a significantly increased risk of unfavourable outcomes.

Patients diagnosed with ER-positive tumours generally have a more favourable prognosis than those with ER-negative tumours for several reasons. Firstly, ER-positive tumours typically respond well to hormone therapy, such as tamoxifen or aromatase inhibitors, which block the effects of oestrogen on cancer cells, slowing or preventing tumour growth and reducing the risk of recurrence. Second, ER-positive tumours tend to be less aggressive and grow more slowly than ER-negative tumours, resulting in a lower likelihood of spreading to distant organs, thus contributing to better overall survival. Lastly, the predictable course of progression and treatment response associated with ER-positive tumours facilitates more effective treatment planning and management.

Progesterone receptor status

Many studies suggest that PR status is a prognostic factor, although its impact may not be as pronounced as that of ER status. Like ER, PR status helps predict a tumour's response to hormone therapy, with positive hormonal status generally indicating a better response to treatment. Progesterone receptor status correlates with other tumour characteristics, such as grade and proliferation rate, which influence the overall prognosis. (17).

Even if the impact of PR status is not statistically significant when controlling for other variables in multivariate analysis, it remains clinically relevant in managing breast cancer. Progesterone receptor status, along with ER status, plays a crucial role in guiding treatment decisions, particularly in the use of hormone therapy.

HER 2 status

HER2-positive breast cancer constitutes approximately 10-20% of primary invasive cases. HER2 positivity has been associated with an increased risk of death and recurrence, as highlighted in studies by Oven Ustaalioglu et al. (10). However, our study yielded different findings. Although Kaplan-Meier survival

analysis showed a trend toward shorter survival for patients with HER2 positive expression compared to those with HER2 negative expression, this difference was not statistically significant (p=0.072). Additionally, Cox regression analysis demonstrated no significant difference in hazard ratios between these two groups. We attribute these findings to the administration of anti-HER2 therapies, specifically trastuzumab (Herceptin). In this study, approximately 43.6% (17 cases) of HER2-positive patients received Herceptin as part of their treatment regimen. The introduction of these therapies has significantly transformed the management of HER2-positive breast cancer, which may have impacted the outcomes observed in our study.

Lymphovascular invasion

Kaplan- Meier analysis showed that positive LVI was statistically significant, indicating worse RFS compared to LVI negative cases (p<0.001). However, when controlling for the effects of other prognostic factors in Cox regression analysis. LVI status was not statistically significant.

This contrasts with the findings of Mahno et al. and Sae R.C. et al., both of whom provided evidence supporting LVI as an independent factor associated with breast cancer recurrence. (3, 8). Discrepancies in research findings may result from various factors, including differences in study populations, methodologies or how LVI was assessed or defined across studies. It is also possible that the relationship between LVI and recurrence is more nuanced and influenced by other factors not accounted for in this study. To resolve these discrepancies, further research is needed to clarify the role of LVI in breast cancer recurrence.

Treatment modality

The analysis did not reveal any statistically significant differences in the type of surgery or other treatments. However, in the multivariable analysis, patients who underwent surgery without receiving any additional treatments showed a higher risk for breast cancer recurrence. Although this result did not reach statistical significance (p = 0.13), it suggests a potential trend toward an increased recurrence risk in this subgroup. This finding is consistent with the research conducted by M. A. O'Rorke in 2016 (18).

CONCLUSION

The investigation of breast cancer recurrence aims to enhance the effectiveness of therapy, improve clinical outcomes, and increase survival rates in breast cancer patients. Several factors, including clinical and pathological characteristics as well as treatment regimens, influence the likelihood of breast cancer recurrence.

This study confirmed the significant associations between breast cancer recurrence and several independent prognostic factors, including higher tumour stage and grade, high lymph node ratio, positive surgical margin, and negative ER status. These findings underscore the importance of personalised treatment strategies tailored to patients with these risk factors. Moreover, regular follow-up examinations are recommended, as close monitoring of high-risk patients enables early interventions and optimises treatment.

This study is limited by its retrospective nature, small sample size from a single centre, and relatively short follow-up duration. The retrospective nature and single-centre setting may have introduced selection bias. Therefore, the results should be validated in a larger, prospective trial to refine the findings and identify new risk factors. Further studies on emerging prognostic and predictive factors, such as the proliferation index (Ki67%), tumour-infiltrating lymphocytes, and PDL-1 immunohistochemical studies, are recommended to further improve clinical treatment decisions.

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